REMARKS

Claims 1-25, 28-30, 33-37, 40-50, 52-54, 107, 252-253 and 258-262 are presently pending in the above-identified patent application. With this Amendment, claims 1, 3-4, 7, 15, 17, 23-24, 29, 35-36, 41, 54, 107 and 259-261 have been amended for clarity and claims 22 and 34 have been cancelled without prejudice. Thus, upon entry of the present Amendment, claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252-253 and 258-262 will be pending.

With this Amendment, claims 1, 54 and 107 have been amended to specify that the first QTL analysis comprises (1) testing for linkages between a plurality of expression statistics for gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis. Support for this amendment is found at step 1910 of Figure 19, page 88, lines 27-34, page 89, lines 6-23, and page 90, lines 4-14, of the specification. Support for this amendment to claims 1, 54, and 107 is also found in Section 5.13, beginning on page 67, line 24, of the specification and Section 5.14, beginning on page 79, line 5, of the specification.

With this Amendment, claim 1 has been further amended to specify that, when the eQTL and the cQTL colocalize to the same locus, gene **G** is deemed to be associated with the clinical trait **T**. Support for this amendment is found on page 92, line 30, through page 95, line 2, as well as step 1914 of Figure 19 of the specification.

With this Amendment, claim 1 has been further amended to specify that the identifying step (A), the identifying step (B) and the determining step (C) are executed using a suitably programmed computer. Support for this amendment is found on page 17, line 15, through page 18, line 2, as well as Figure 1 of the specification which describes a system 10 that is operated in accordance with an embodiment of the invention.

With this Amendment, claims 23 and 35 have been amended to specify that the testing generates a statistical score for said position in the genome of said species. Support for this amendment is found on page 89, lines 24-33, of the specification.

With this Amendment, claim 54 has been amended to specify executable instructions for performing a method that comprises an identifying step (A), an identifying step (B) and a determining step (C). Support for this amendment to claim 54 is found in Section 5.1, beginning on page 17, line 14, of the specification. In particular, page 17, line 15, through page 18, line 2, as well as Figure 1 of the specification describes a system 10, which includes

a central processing unit 22, that is operated in accordance with an embodiment of the invention. Support for this amendment to claim 54 is also found in Section 5.16 beginning on page 86, line 13, of the specification as well as Figure 19 of the specification. In particular, page 88, line 27, through page 91, line 25, as well as step 1910 of Figure 19 of the specification describe the identifying step (A), page 91, line 26, through page 92, line 29, as well as step 1912 of Figure 19 of the specification describe the identifying step (B), and page 92, line 30, through page 95, line 2, as well as step 1914 of Figure 19 of the specification describe the determining step (C).

With this Amendment, claim 107 has been amended to specify a memory, coupled to the central processing unit, the memory storing one or more programs that cause the central processing unit to perform a method comprising an identifying step (A), an identifying step (B) and a determining step (C). Support for this amendment to claim 107 is found in Section 5.1, beginning on page 17, line 14, of the specification. In particular, page 17, line 15, through page 18, line 2, as well as Figure 1 of the specification describes a system 10, which includes a central processing unit 22, that is operated in accordance with an embodiment of the invention. Support for this amendment to claim 107 is also found in Section 5.16 beginning on page 86, line 13, of the specification as well as Figure 19 of the specification. In particular, page 88, line 27, through page 91, line 25, as well as step 1910 of Figure 19 describe the identifying step (A), page 91, line 26, through page 92, line 29, as well as step 1912 of Figure 19 describe the identifying step (B), and page 92, line 30, through page 95, line 2, as well as step 1914 of Figure 19 describe the determining step (C).

With this Amendment, claim 259, which specifies a null hypothesis that deems an eQTL and a cQTL to be represented by a QTL that is common to both the eQTL and cQTL in a test for pleiotropy, has been amended to specify that Q categorically indicates the genotype at the position of the eQTL and the cQTL and that $\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ has a bivariate normal random distribution. Support for these amendments to claim 259 is found in the specification at page 93, line 10, through page 94, line 4.

With this Amendment, claims 260 and 261, which specify an alternative hypothesis that deems there to be linkage disequilibrium in a test for pleiotropy, have been amended to specify that Q_1 and Q_2 categorically indicate the genotypes at the positions of the eQTL and the cQTL, respectively, and that $\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ has a bivariate normal random distribution. Support

for these amendments to claims 260 and 261 is found in the specification at page 93, lines 10-17, and page 94, lines 2-21.

The specification has been amended to (i) inactivate all hyperlinks and/or other forms of browser-executable code, (ii) correct and use consistent format for reference citations, (iii) remove references to websites that no longer exist on the Internet, and (iv) correct typographical errors. Support for the amendment to the citation to Lander and Botstein, 1989, Genetics 121: 185-199 made in the paragraph beginning on page 71, line 27, of the specification is found in the paragraph beginning on page 74, line 3, of the specification.

Accordingly, no new matter has been added by way of the amendments to the claims and the specification. Entry of the foregoing amendments is respectfully requested.

THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The Examiner has objected to the specification because it contains embedded hyperlinks and other forms of browser-executable code. The objection to the specification has been addressed hereinabove by amending the specification to inactivate all hyperlinks and other forms of browser-executable code. Accordingly, Applicants respectfully request that the objection to the specification be withdrawn.

THE 35 U.S.C. § 101 REJECTION SHOULD BE WITHDRAWN

In point 5 of the February 12, 2009 Office Action, the Examiner rejected claims 1-25, 28-30, 33-37, 40-50, 52-53, 252-253 and 258-262 under 35 U.S.C. § 101 because the claims are allegedly directed to non-statutory subject matter. In point 6 of the February 12, 2009 Office Action, the Examiner rejected claims 1-25, 28-30, 33-37, 40-50, 52-54, 107, 252-253 and 258-262 under 35 U.S.C. § 101 because the claims are allegedly directed to non-statutory subject matter. In point 7 of the February 12, 2009 Office Action, the Examiner rejected claim 54 under 35 U.S.C. § 101 because the claim is allegedly directed to non-statutory subject matter. Applicants traverse the 35 U.S.C. § 101 rejections made in points 5 through 7 of the February 12, 2009 Office Action and collectively address these rejections in the remarks hereinbelow as they apply to claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-53, 252-253 and 258-262. Claims 22 and 34 have been cancelled without prejudice and thus the rejection as applied to these claims is moot.

Citing *State St. Bank & Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), the Board of Patent Appeals and Interferences in *Ex parte Bo Li*, 2008 Pat.

App. LEXIS 27; __ U.S.P.Q. 2d ____, 2008-1213 (B.P.A.I., 2008) stated that '[t]he test for statutory subject matter is whether the claimed subject matter is directed to a "practical application." See, *Ex parte Bo Li*, 2008 Pat. App. LEXIS 27 at *4.

In re Bilski, 545 F.3d 943 (Fed. Cir. 2008) held that the test for determining whether claims are patentable subject matter under 35 U.S.C. § 101 is the machine-or-transformation test. See *In re Bilski*, 545 F.3d at 954 ("[a] claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing"). Thus, a claim is patentable subject matter under 35 U.S.C. § 101 if the claim is tied to a particular machine or apparatus or the claim involves the transformation of a particular article into a different state or thing.

Claims 1, 54 and 107 Satisfy the Machine Prong of the *In re Bilski* Machine-or-Transformation Test

Claim 1, as amended, specifies a method that requires executing, using a suitably programmed computer, an identifying step (A), an identifying step (B) and a determining step (C). Therefore, the method of claim 1 is tied to a particular machine or apparatus and claim 1 satisfies the machine prong of the *In re Bilski* machine-or-transformation test.

Claim 54, as amended, specifies a computer program product comprising a computer readable storage medium and a computer readable program mechanism embedded therein. Claim 54, as amended, specifies that the computer program mechanism comprises executable instructions for performing the recited method, comprising an identifying step (A), an identifying step (B) and a determining step (C). The instant specification makes it clear that a computer readable storage medium is a tangible thing (an apparatus). The instant specification provides examples of computer readable storage media in Section 5.1, beginning on page 17, line 14, of the specification as well as Figure 1 such as memory 24 (page 17, lines 21-22, and Figure 1). As such, claim 54 is limited to physical forms of computer readable media and does not read on embodiments that are not physical computer readable media that are conventional in the art. Therefore, the executable instructions of claim 54 are tied to a particular machine or apparatus (the computer readable storage medium) and claim 54 satisfies the machine prong of the *In re Bilski* machine-or-transformation test.

Claim 107, as amended, specifies a computer system comprising a central processing unit and a memory coupled to the central processing unit. The memory stores one or more

programs that cause the central processing unit to perform the recited method, comprising an identifying step (A), an identifying step (B) and a determining step (C). Therefore, the method recited in claim 107 is tied to a particular machine or apparatus and satisfies the machine prong of the *In re Bilski* machine-or-transformation test.

Claims 1, 54 and 107 Satisfy the Transformation of Matter Prong of the *In re Bilski* Machine-or-Transformation Test

Claims 1, 54 and 107 also satisfy the transformation prong of the machine-or-transformation test for patentable subject matter set forth in *In re Bilski*. See *In re Bilski*, 545 F.3d at 954. A claimed process satisfies the transformation prong of the machine-or-transformation test for patentable subject matter if the process transforms or reduces an article, or an electronic signal representative of any physical object or substance, into a different state or thing. See *In re Bilski*, 545 F.3d at 963-964.

Claims 1, 54 and 107 specify methods that transform a plurality of expression statistics for a gene **G** into an expression quantitative trait loci (eQTL) for the gene. As such, the eQTL for the gene clearly represents a transformation of an article (a plurality of expression statistics for a gene **G**) into a different state or thing (the eQTL). Claims 1, 54 and 107 further specify methods that transform a plurality of phenotypic values for a clinical trait **T** into a clinical quantitative trait loci (cQTL) that is linked to the clinical trait **T**. As such, the cQTL that is linked to the clinical trait **T** clearly represents a transformation of an article (a plurality of phenotypic values for a clinical trait **T**) into a different state or thing (the cQTL).

Claims 1, 54 and 107 Have Substantial Practical Application

Claims 1, 54 and 107 are also patentable under 35 U.S.C. § 101 because the identification of whether an eQTL and a cQTL colocalize to the same locus in the genome of a species, as specified in claims 1, 54 and 107, has substantial practical application. In claims 1, 54 and 107, the useful result, the determination as to whether gene **G** is deemed associated with clinical trait **T**, is clearly stated. As stated in claims 1, 54 and 107, colocalization of the eQTL and the cQTL serves as the basis for deeming a given gene **G** to be associated with a clinical trait **T**. As is appreciated by those of skill in the art, methods for associating a given gene **G** with a clinical trait **T** are expected to give rise to a further understanding of molecular basis for the clinical trait **T** and thus, ultimately, improved treatment.

The specification provides ample teaching of the efforts made by those of skill in the art to associate genes with clinical traits and thus evidences that such workers will recognize what the results of the methods specified in claims 1, 54 and 107 mean (and thus how they can be used). For example, the instant specification states:

> A variety of approaches have been taken to identify genes and pathways that are associated with traits, such as human disease. In one approach, attempts have been made to use gene expression data to identify genes and pathways associated with such traits. In another approach, genetic information has been used to attempt to identify genes and pathways associated with traits. For instance, clinical measures of a population cab [*sic*] be taken to study a trait such as a disease found in the population. Risk factors for the trait can be established from these clinical measures. Demographic and environmental factors are further used to explain variation with respect to the trait. Further, genetic variations associated with traits, such as disease-related traits, as well as the disease itself are used to identify regions in the genome linked to a disease. For example, genetic variations in a population may be used to determine what percentage of the variation of the trait in the population of interest can be explained by genetic variation of a single nucleotide polymorphism (SNP), haplotype, or short tandem repeat (STR) marker. However, as will be described below, the elucidation of genes involved in biological pathways that influence a trait, such as a disease, using either gene expression or genetic expression approaches, is problematic and generally not successful in many instances.
>
> Specification, page 1, lines 16-31.

Thus, the specification provides ample teaching for one of skill in the art to recognize the practical application provided by the identification of whether an eQTL and a cQTL colocalize to the same locus in the genome of a species in the manner specified by claims 1, 54 and 107. Each of the remaining rejected claims ultimately depends from claim 1 and are thus patentable under 35 U.S.C. § 101 for at least the same reasons as claim 1.

For the foregoing reasons, Applicants respectfully submit that the 35 U.S.C. § 101 rejection of claims 1-21, 23-25, 28-30, 33, 35-37, 40-50, 52-54, 107, 252-253 and 258-262 should be withdrawn.

THE 35 U.S.C. § 112, SECOND PARAGRAPH, REJECTION SHOULD BE WITHDRAWN

The Examiner has rejected claims 259-261 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because not all variables are defined. In response, claim 259, which

specifies a null hypothesis that deems an eQTL and a cQTL to be represented by a QTL that is common to both the eQTL and cQTL in a test for pleiotropy, has been amended to specify that Q categorically indicates the genotype at the position of the eQTL and the cQTL and that $\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ has a bivariate normal random distribution. Further, claims 260 and 261, which specify an alternative hypothesis that deems there to be linkage disequilibrium in a test for pleiotropy, have been amended to specify that Q_1 and Q_2 categorically indicate the genotypes at the positions of the eQTL and the cQTL, respectively, and that $\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ has a bivariate normal random distribution. Accordingly, Applicants respectfully request that the 35 U.S.C. § 112, second paragraph, rejections of claims 259-261 be withdrawn.

THE 35 U.S.C. § 102 REJECTION SHOULD BE WITHDRAWN

Claims 1-2, 5-11, 42-44, 49-50, 52-53, 252 and 258 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Aitman *et al.*, 1999, Nature Genetics 21, 76-83 (hereinafter, "Aitman"). Applicants traverse the rejection.

Claim 1, as amended, specifies identifying an expression quantitative trait loci (eQTL) for a gene **G** using a first quantitative trait loci (QTL) analysis, where the first QTL analysis uses a plurality of expression statistics for gene **G** as a quantitative trait, where each expression statistic in the plurality of expression statistics represents an expression value for gene **G** in an organism in said plurality of organisms. Claim 1, as amended, further specifies that the first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for gene **G** and locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis.

Aitman does not disclose, teach or suggest a first quantitative trait loci (QTL) analysis that comprises (1) testing for linkages between a plurality of expression statistics for gene **G** and locations along a genetic map of the plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis. Aitman notes that QTL linkages for hypertension, hypertriglyceridaemia, reduced high density lipoprotein (HDL) phopholipid

and the metabolic defects in adipocytes map to a single region close to the telomere of rat chromosome 4. *See* Aitman, page 76, left column, last paragraph.

The region identified by Aitman on rat chromosome 4 is a clinical quantitative trait loci (cQTL), not an expression quantitative trait loci (eQTL). As set forth on page 7, lines 20-24, of the specification, an eQTL is identified using a plurality of expression statistics for a gene **G**, where each expression statistic in the plurality of expression statistics represents an expression value for gene **G** in an organism in a plurality of organisms. As set forth on page 7, lines 24-28, of the specification, a cQTL is identified using a plurality of phenotypic values as a quantitative trait, where each phenotypic value in the plurality of phenotypic values represents a phenotypic value for a clinical trait **T** in an organism in a plurality of organisms. Thus, the Aitman quantitative analysis does not disclose, teach or suggest identifying an eQTL as required by the rejected claims.

To narrow the chromosome 4 cQTL interval, Aitman phenotyped a new (SHRxWistar Kyoto (WKY)) F2 cross (n=227) for insulin-mediated glucose uptake and catecholamine-mediated lipolysis and determined the genotypes of these animals for markers on chromosome 4. This work resulted in the identification of a cQTL (with a lod score of 8.8 for defective catecholamine action and a lod score of 4.0 for defective insulin action) that colocalizes with the microsatellite marker *D4Bro1*. *See* Aitman, paragraph bridging pages 76-77. Note that, here again, as was the case in the Aitman experiment described hereinabove, because a plurality of phenotypic values was used as the quantitative trait, where each phenotypic value in the plurality of phenotypic values represents a phenotypic value for a clinical trait **T** (insulin-mediated glucose uptake and catecholamine-mediated lipolysis), the interval identified in the paragraph bridging pages 76-77 of Aitman is a cQTL, not an eQTL, and thus does not disclose, teach or suggest identifying an eQTL as required by the rejected claims.

To further characterize the phenotype and to facilitate gene identification, Aitman created a congenic strain for chromosome 4 (SHR.4) in which the region of the chromosome 4 QTL containing the microsatellite marker *D4Bro1*was replaced with a corresponding region from Brown Norway (BN) genome, with the remainder of the genome derived from the SHR progenitor strain in which the QTL was discovered. The SHR.4 strain showed partial correction of the insulin-mediated glucose update defect of the SHR strain and full correction of the isoproternol-mediated lipolysis defect in the SHR strain. *See* Aitman, page 77, left column, last paragraph as well as Figures 1a and 1b on the top of page 77.

Aitman sought genes that were differentially expressed between the SHR strain and insulin-sensitive controls (BN and SHR.4 strains). *See* Aitman, page 77, right column. This work resulted in the identification of three clones encoding rat *Cd36* that showed reduced hybridization signals (greater than 90%) for SHR compared with those of BN and SHR.4. *See* Aitman, page 77, right column, last paragraph and Figures 2a and 2b on the bottom of page 77. These differential expression experiments are the only experiments in Aitman that make use of expression statistics for rat *Cd36*. However, the Aitman differential expression experiments do not identify a quantitative trait loci (QTL), much less an expression quantitative trait loci (eQTL), for rat *Cd36* by (1) testing for linkages between a plurality of expression statistics for rat *Cd36* and locations along a genetic map of the rat genome, or (2) comparing genotype data from each rat in a plurality of rats to the plurality of expression statistics for rat *Cd36* using allelic association analysis, as required by claim 1, as amended. The Aitman gene expression profiling experiments do not even identify the location of a QTL for rat *Cd36* in the rat genome.

Aitman infers that rat *Cd36* is on rat chromosome 4 through syntenic data from humans and rats. Aitman confirms the inference drawn from the syntenic data using PCR to detect chromosomal fragments that retain Cd36 in a rat/hamster recombinant hybrid panel. Using this PCR analysis, Aitman maps rat *Cd36* to a location on rat chromosome 4 that is approximately 2.5 to 5 cm away from the microsatellite marker *D4Bro1*. *See* Aitman, page 78, left column, in the section entitled "RH mapping localizes *Cd36* to the chromosome 4 QTL" and Figure 3 at the top of page 78. As was the case in the Aitman differential expression experiment, the Aitman PCR experiment does not disclose, teach or suggest (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended.

Aitman also confirms the genomic location of *Cd36* using linkage analysis based on a *Hinf1* restriction fragment length polymorphism (RFLP). The *Hinf1* site giving rise to this RFLP is present, for example, in cDNA encoding *Cd36* from the SHR rat strain but not in cDNA encoding *Cd36* from the WKY or BN rat strains. *See* Aitman, page 78, right column, in the section entitled "Localization of *Cd36* by linkage analysis" and Figure 7a at the top of page 80. However, this and other linkage analyses described in this section of Aitman as well as the section entitled "Linkage of Cd36 to defective insulin and catecholamine action" in the

left column on page 79 of Aitman do not disclose, teach or suggest (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended. Each linkage analysis discussed in the section entitled "Localization of *Cd36* by linkage analysis" on page 78 of Aitman and the section entitled "Linkage of Cd36 to defective insulin and catecholamine action" in the left column on page 79 of Aitman and illustrated in Figures 7a and 7b at the top of page 80 of Atiman does not make use of a plurality of expression statistics for a gene **G** as required by claim 1 and thus does not anticipate claim 1. As set forth on page 7, lines 22-24, of the specification, each expression statistic in a plurality of expression statistics represents an expression value for a gene **G** in an organism in a plurality of organisms.

The direct sequencing and related experiments disclosed in the section entitled "Sequence variation in *Cd36* cDNA" that bridges the left and right hand column on page 78 of Aitman and that are illustrated in Figures 4a and 4b on page 78 of Aitman, Figure 5 on the top of page 79 of Aitman, and Figures 6a and 6b on the bottom of page 79 of Aitman also do not disclose, teach or suggest testing (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended.

The direct sequencing and Southern-blot experiments disclosed in the section entitled "Duplication and deletion of *Cd36*" that bridges the left and right hand column on page 79 of Aitman and that are illustrated in Figures 7c and 7d on page 80 of Aitman also do not disclose, teach or suggest (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended.

The northern-blot analysis of *Cd36* expression in SHR and control strains, and the copy-specific restriction digestion of *Cd36*, disclosed in the section entitled "Expression of *Cd36* in SHR" that bridges pages 79 and 80 of Aitman and that are illustrated in Figures 8a and 8b on page 81 of Aitman, and the western-blot analysis of SHR microsomal pellets disclosed in the section entitled "Cd36 is undetectable in SHR plasma membrane" in the

section bridging the left and right hand columns on page 80 of Aitman and illustrated in Figure 8c on page 81 of Aitman also do not disclose, teach or suggest (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended.

Claims 2, 5-11, 42-44, 49-50, 52-53, 252 and 258 ultimately depend from claim 1 and thus are patentable over Aitman for at least the same reasons that claim 1 is patentable over Aitman. Accordingly, Applicants respectfully request that the 35 U.S.C. § 102(b) rejection of claims 1-2, 5-11, 42-44, 49-50, 52-53, 252 and 258 be withdrawn.

THE 35 U.S.C. § 103(a) REJECTION OF CLAIMS 1 AND 12-16 SHOULD BE WITHDRAWN

Claims 1 and 12-16 have been rejected under 35 U.S.C. § 103(a) as being obvious in view of Aitman. Applicants traverse the rejection. As discussed hereinabove in response to the 35 U.S.C. § 102(b) rejection of claim 1 over Aitman, Aitman does not disclose, teach, suggest, or provide reason to perform, (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended. Claims 12-16 ultimately depend from claim 1 and thus are patentable over claim 1 for at least the same reason that claim 1 is patentable over Aitman. Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 1 and 12-16 be withdrawn.

THE 35 U.S.C. § 103(a) REJECTION OF CLAIMS 1, 3-4, 17-25, 33-37, 40-41 AND 45-49 SHOULD BE WITHDRAWN

Claims 1, 3-4, 17-25, 33-37, 40-41 and 45-49 have been rejected under 35 U.S.C. § 103(a) as being obvious in view of Aitman in view of Dominiczak *et al.*, 2000, Hypertension Volume 35 (part 2), 165-172 (hereinafter, "Dominiczak"). The rejection is moot with respect to claims 22 and 34 because these claims have been cancelled without prejudice. Applicants traverse the rejection as it applies to claims 1, 3-4, 17-21, 23-25, 33, 35-37, 40-41 and 45-49.

As discussed hereinabove in response to the 35 U.S.C. § 102(b) rejection of claim 1 over Aitman, Aitman does not disclose, teach, suggest, or provide a reason to perform, (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended.

Dominiczak, which discloses cQTL for hypertension that are identified using blood pressure subphenotypes and cardiovascular complications, such as left ventricular hypertrophy, kidney failure, and stroke, does not remedy the deficiencies in Aitman. Dominiczak does not disclose, teach, suggest, or provide a reason to perform a QTL analysis that uses a plurality of expression statistics for gene **G** as a quantitative trait. The QTL identified by Dominiczak are cQTL because the blood pressure and cardiovascular phenotypes are phenotypic values for clinical traits **T** in an organism in a plurality of organisms rather than expression values for a gene **G** in organisms in a plurality of organisms. Thus, claim 1 is patentable over the combination of Aitman and Dominiczak. Claims 3-4, 17-25, 33-37, 40-41 and 45-49 ultimately depend from claim 1 and thus are patentable over claim 1 for at least the same reason that claim 1 is patentable over the combination of Aitman and Dominiczak. Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 1, 3-4, 17-25, 33-37, 40-41 and 45-49 be withdrawn.

THE 35 U.S.C. § 103(a) REJECTION OF CLAIMS 54, 107, 253, AND 262 SHOULD BE WITHDRAWN

Claims 54, 107, 253 and 262 have been rejected under 35 U.S.C. § 103(a) as being obvious in view of Aitman in view of Manly *et al.*, 1999, Mammalian Genome 10, 327-334 (hereinafter, "Manly"). Applicants traverse the rejection. As discussed hereinabove in response to the 35 U.S.C. § 102(b) rejection of claim 1 over Aitman, Aitman does not disclose, teach, suggest, or provide a reason to perform, (1) testing for linkages between a plurality of expression statistics for a gene **G** and locations along a genetic map of a plurality of organisms, or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis as required by claim 1, as amended.

Like claim 1, claims 54 and 107 require (1) testing for linkage between a genotype of a plurality of organisms at a position in the genome of a species and a plurality of expression statistics for gene **G** or, (2) using allelic association analysis to compare genotype data for a genetic marker from each organism in the plurality of organisms to the plurality of expression statistics for gene **G** using allelic association analysis. Thus, claims 54 and 107 are each patentable over Aitman for at least the same reason that claim 1 is patentable over Aitman.

Manly, which is directed to an overview of QTL mapping software and an introduction to the software program Map Manager QT, does not remedy the deficiencies in Aitman. Manly does not disclose identifying eQTL using a plurality of expression statistics for a gene **G**, where each expression statistic in the plurality of expression statistics represents an expression value for gene **G** in an organism in a plurality of organisms. Thus, claims 1, 54 and 107 are patentable over the combination of Aitman and Manly. Claims 253 and 262 ultimately depend from claim 1 and thus are patentable over the combination of Manly and Aitman for at least the same reason that claim 1 is patentable over the combination of Manly and Aitman. Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 54, 107, 253 and 262 be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. If any fees are due in connection with this submission, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: August 6, 2009

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